FDA's Statutory Framework and the Evaluation of Pharmaceuticals for Potential Environment Impacts

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Statutory Framework

- Federal Food, Drug, and Cosmetic Act (FFDCA)
- National Environmental Policy Act (NEPA)

Federal Food, Drug, and Cosmetic Act

FFDCA requires FDA to approve a drug if FDA finds that none of the grounds for denying approval apply

Federal Food, Drug, and Cosmetic Act

Grounds for denying approval, for example:

- Lack of substantial evidence that the drug will have the effect it claims to have

- There is insufficient information to show that the drug is safe for use under the conditions included in the labeling

CDER Mission

To ensure that safe and effective drugs are available to the American people

National Environmental Policy Act

- Requires all Federal agencies to assess the environmental impacts of their actions
- Under NEPA, FDA considers the environmental impacts of approving drugs

National Environmental Policy Act

- The NEPA process is intended to help public officials make decisions that are based on the understanding of environmental consequences, and take actions that protect, restore, and enhance the environment

- However, NEPA does not require that the most environmentally beneficial course of action be taken

Statutory Framework

- FDA must operate within the statutory framework of the FFDCA and NEPA
- If FFDCA and NEPA conflict, NEPA gives way

NEPA Process

- Categorical Exclusion (CE)
- Environmental Assessment (EA)
- Environmental Impact Statement (EIS)

Categorical Exclusion

Classes of actions that individually or cumulatively do not significantly affect the quality of the human environment are ordinarily excluded from the requirement to prepare an EA or EIS

Categorical Exclusion

FDA requires at least an EA for any specific action that ordinarily would be excluded if **extraordinary circumstances** indicate that the specific proposed action may significantly affect the quality of the human environment

Categorical Exclusion

Actions normally categorically excluded include those relating to:

- Investigational new drug applications (INDs)
- New drug applications (NDAs) or abbreviated new drug applications (ANDAs) when the approval will not increase the use of the drug or the concentration of drug expected to enter the aquatic environment (EIC) is less than 1 ppb

Environmental Assessment

A concise document that provides sufficient information to determine whether an EIS or finding of no significant impact (FONSI) should be prepared

Environmental Assessment

Actions normally requiring an EA include:

- Approval of an NDA or efficacy supplements when the approval will increase the use of the drug and the concentration of drug expected to enter the aquatic environment (EIC) is 1 ppb or greater

- Approval of an NDA or ANDA when the drug is derived from wild plants or animals (extraordinary circumstance provision)

Environmental Impact Statement

There are no categories of FDA actions that routinely significantly affect the quality of the human environment and that therefore ordinarily require the preparation of an EIS

Environmental Impact Statement

- FDA has prepared only one EIS directly related to drug use (CFCs, 1978)
- One application referenced an EIS prepared by the USDA, Forestry Service

Typical Environmental Issues in EAs for Human Drugs

- EIC ≥ 1 ppb (toxicity)
- Use of wild plants or animals (harvesting)

Toxicity Evaluation

- Fate
- Effects

Fate: Physical/Chemical Characterization

- Water solubility
- Dissociation constant
- Octanol/water partition coefficient
- Vapor pressure
- Sorption/desorption properties

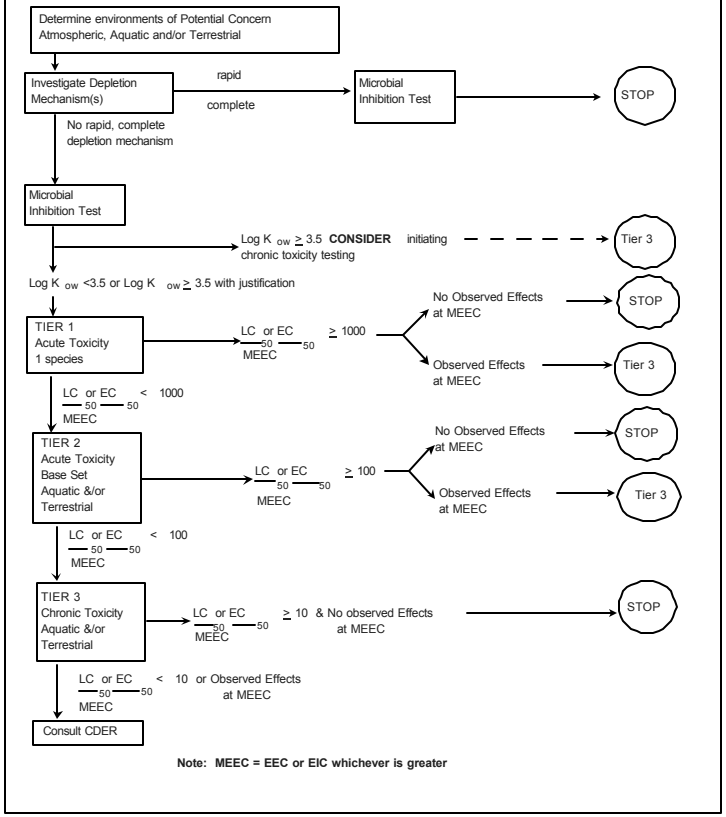
Fate: Depletion Mechanisms

- Photolysis
- Hydrolysis
- Biodegradation

Effects

- Tiered approach; starting with acute testing
- Recommends aquatic test organisms over terrestrial
- Based on EPA approach

Figure 1
Tiered Approach to Fate and Effects Testing



Note: MEEC = EEC or EIC whichever is greater

REGO and 1 ppb

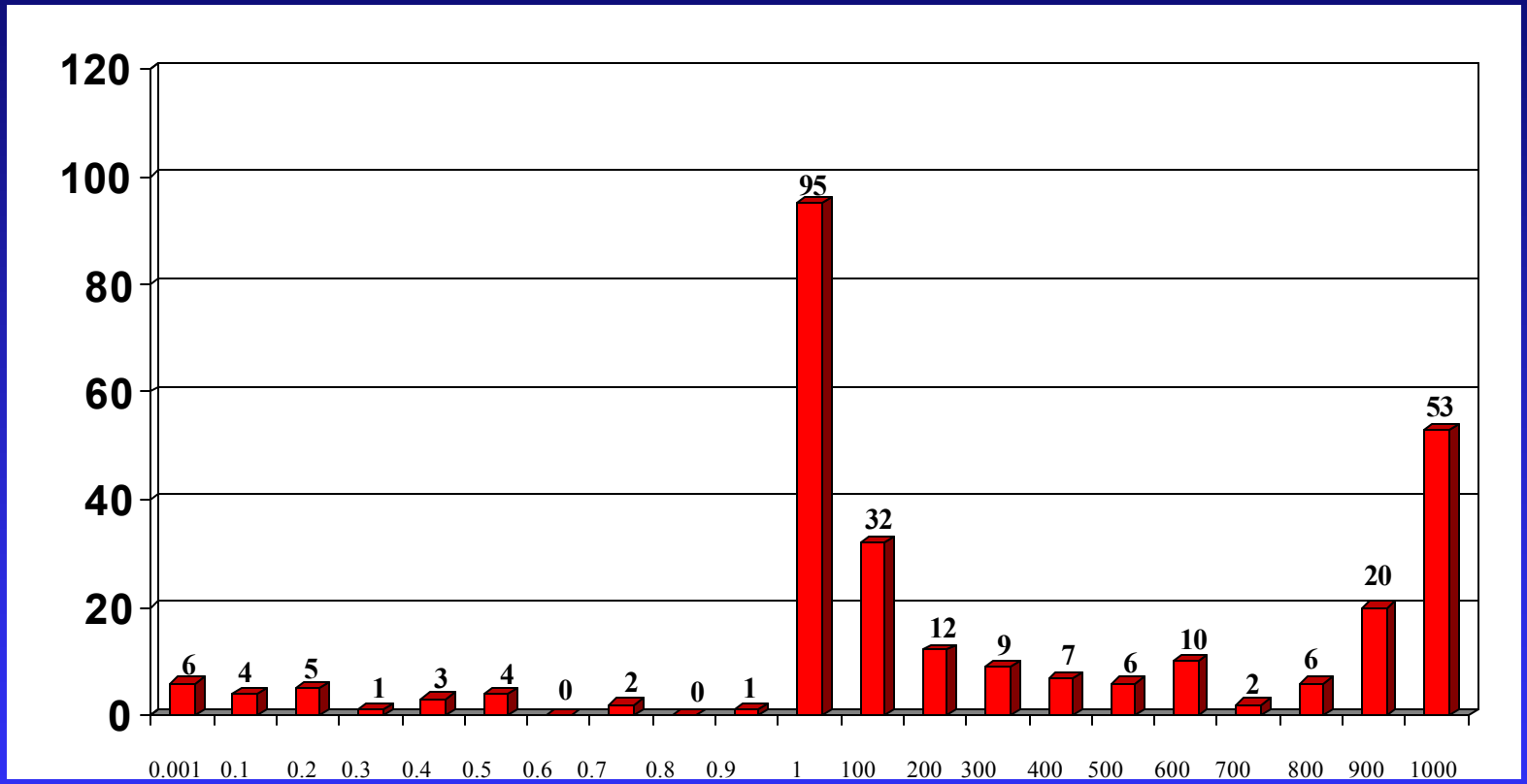
- In April 1995, the President announced his Reinventing Government Initiatives (REGO)
- Since all CDER EAs had resulted in FONSIs, REGO proposed to increase the number of categorical exclusions from EA and EIS requirements

REGO and 1 ppb

- To support the REGO initiative FDA performed a retrospective data review
- FDA published the final rule revising its NEPA regulations July 1997

Retrospective Review of Ecotoxicity Data

Center for Drug Evaluation and Research (CDER)



Toxicity test result (ppm)

1 ppb

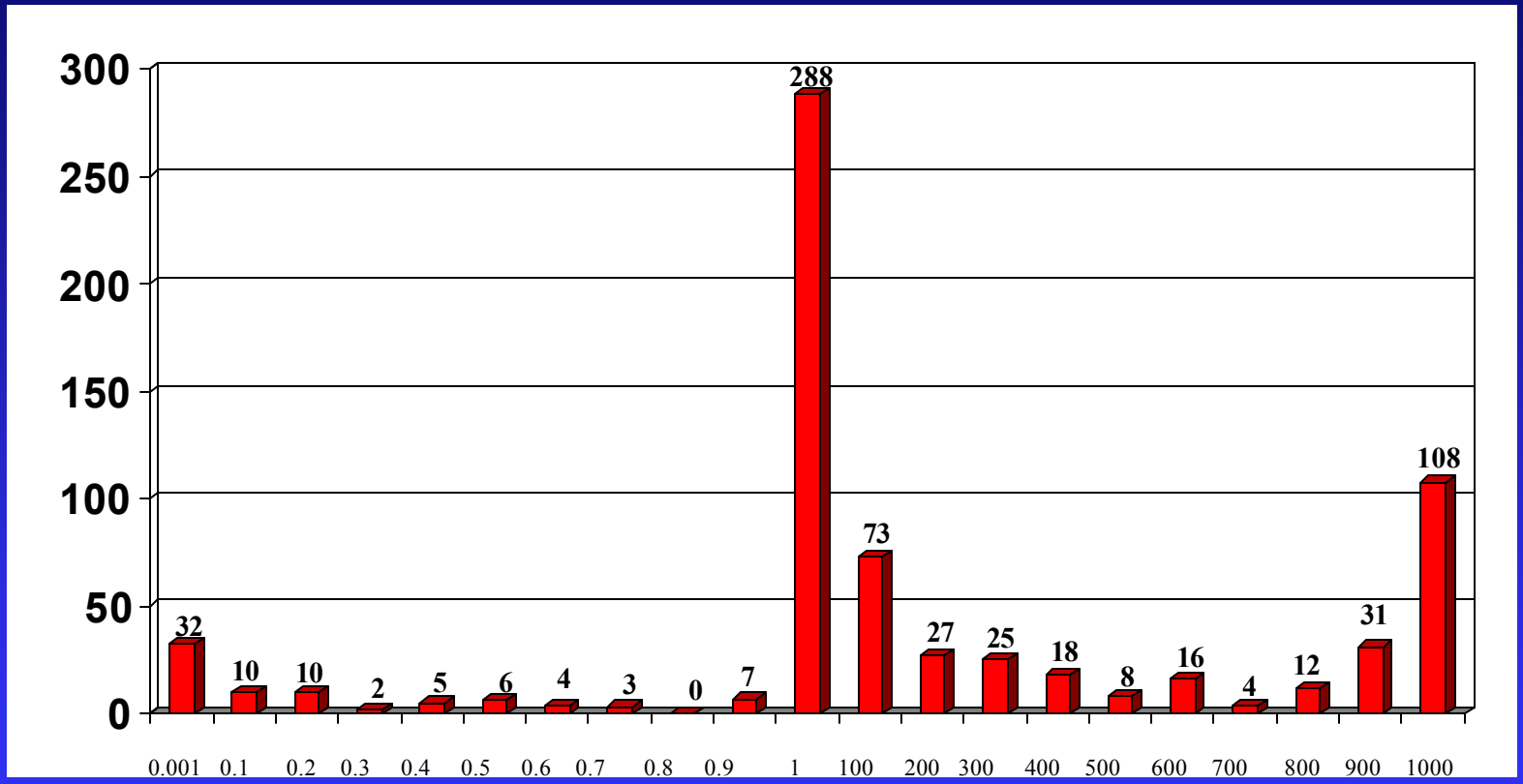
- Data routinely demonstrated no effects on relevant standard test organism at concentration less than 1 ppb
- Approximately 90% of the toxicity results were 1 ppm or greater
- Approximately 10% of the toxicity results were between 1 ppb and 1 ppm

1 ppb

- Of those between 1 ppb and 1 ppm approximately 1/3 were antibiotics and 1/3 were central nervous system drugs
- Toxicity test concentration ranges are often limited by the solubility of the drug (i.e., NOEC or LC_{50}/EC_{50} may really be higher than reported)

Retrospective Review of Ecotoxicity Data

Note: 10 Values in the pptr range; 9 from one drug



Toxicity test result (ppm)

Summary

Based on currently accepted approaches/procedures, evaluation of the toxicity of drugs to environmental organisms when the EIC is less than 1 ppb, absent extraordinary circumstances, will not provide information that is useful in CDER's decision making process.

From CEQ Regulations...

"Ultimately, of course, it is not better documents but better decisions that count. NEPA's purpose is not to generate paperwork — even excellent paperwork — but to foster excellent action.

Sources of Information

- 21 CFR Part 25 (FDA regulations implementing NEPA)
- 40 CFR Parts 1500-1508 (NEPA regulations)
- 40 CFR Parts 796-797 (EPA Tests)

Sources of Information

- FDA's guidance on *Environmental Assessment of Human Drug and Biologics Applications* (July 1998) available at http://www.fda.gov/cder/guidance/index.htm

- *Retrospective Review of Ecotoxicity Data Submitted in Environmental Assessments* available under FOI from Public Docket No. 96N-0057